Exhibit B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Shi, et al.
Serial No.	:	09/438,206
Group Art Unit	:	1617
Examiner	:	S. Hui
Filed	:	November 12, 1999
For	:	Methods and Compositions for Treating Mammalian Spinal Cord Injuries

Commissioner for Patents
Washington, D. C. 20231

Amendment After Final Action

Sir:

In response to the Office Action of November 23, 2001, please amend the application as follows. (Changes shown in APPENDIX A.) In addition, please consider the observations made below with respect to the patentability of the claimed invention.

In the Claims:

Amend claim 22 to read as follows:

22. (Once Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting the injured spinal cord within a period no greater than about 24 hours after said injury with a C_1-C_{10} polyalkylene glycol in an amount effective to increase a compound action potential in said injured spinal cord relative to a level of said compound action potential immediately after said injury and to increase behavioral recovery after said spinal cord is treated.

Amend claim 30 to read as follows:

30. (Once Amended) The method according to claim 22, wherein said polyalkylene glycol is polyethylene glycol and wherein said method further

comprises the step of contacting said injured spinal cord with a potassium channel blocker in the form of 4-aminopyridine in an effective amount and within an effective time of contacting said spinal cord with said polyethylene glycol so as to produce a synergistic increase in restoration of nerve function and reflex behavior in said patient.

Cancel claims 31-37.

Amend claim 38 to read as follows:

32. (Once Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting the injured spinal cord within a period no greater than about 24 hours after said injury with polyethylene glycol in an amount effective to increase a compound action potential in said injured spinal cord relative to a level of said compound action potential immediately after said injury and to increase behavioral recovery after said spinal cord is treated.

Amend claim 40 to read as follows:

40. (Once Amended) The method according to claim 38 further comprising the step of contacting said injured spinal cord with a potassium channel blocker in the form of 4-aminopyridine in an effective amount and within an effective time of contacting said spinal cord with said polyethylene glycol.

Cancel claims 41 and 42.

REMARKS

After amendment, claims 22-30, 38-40 and 43 are pending in the present application. Claims 31-37, 41 and 42 are cancelled herein. Claims 1-21 were cancelled previously *without prejudice*.

Claims Rejections – 35 U.S.C. § 112, First Paragraph

Claims 30-37 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification is purportedly lacking in enablement for combinations of C_3-C_{10} polyalkylene glycols and potassium channels blockers other than 4-aminopyridine.

In response to the rejection of claims 30-37 under 35 U.S.C. § 112, first paragraph, claim 30 has been amended to limit the claimed synergistic combination to that of polyethylene glycol and 4-aminopyridine, while claims 31-37 have been cancelled.

Claims Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 22-43 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner specifically maintains that the recitation "said method resulting in ... after said spinal cord is treated" in claim 22, lines 4-6 and claim 38, lines 2-6, is indefinite as to the method steps required to achieve the recited results.

In response to this rejection of claims 22 and 38, those claims have been amended to clarify the steps required to achieve the recited results. In particular, claims 22 and 38 have been amended to recite that the claimed polyalkyene glycol is applied "in an amount effective to increase a compound action potential in said injured spinal cord relative to a level of said compound action potential immediately after said injury and to increase behavioral recovery after said spinal cord is treated." It is therefore clear that the application of a therapeutically effective amount is the step necessary to achieve the desire results.

With respect to claims 22 and 38, the Examiner also points out that the expression "as soon as possible" renders those claims indefinite as to the time of contact between the injured spinal cord and the polyalkylene compounds encompassed by the claims.

In response to this point, claims 22 and 38 have been amended to delete the phrase "as soon as possible." The time of contact is now clearly specified.

With reference to claim 30, the Examiner contends that the recitation "said method resulting in a synergistic increase ... behavior in said patient" in lines 4-6 renders the claim indefinite as to the method steps required to achieve the recited results.

In response to this rejection of claim 30, that claim has been amended to clarify the steps required to achieve the recited results. In particular, claim 30 has been amended to recite "contacting said injured spinal cord with a potassium channel blocker ... so as to produce a synergistic increase in restoration of nerve function and reflex behavior in said patient." Thus, the recited synergistic increase is produced by the contacting of the injured spinal cord with the potassium channel blocker.

With reference to claims 30 and 40, the Examiner contends that the expression "before, during or after contacting said spinal cord with said polyalkylene glycol" renders the claims indefinite.

In response to this rejection of claims 30 and 40, those claims have been amended to recite that the contacting the spinal cord with the potassium channel blocker is within an effective time of contacting the spinal cord with polyethylene glycol so as to produce a synergistic increase in restoration of nerve function and reflex behavior in the patient. The timing of application of the potassium channel blocker is therefore tied to the effectiveness of the application.

With respect to claims 22 and 38, the Examiner maintains that the phrase "at least partial restoration" is a relative term which renders the claims indefinite. According to the Examiner, the phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In response to this rejection of claims 22 and 38, those claims have been amended to eliminate the phrase "at least partial restoration" and to refer instead to the increase in compound action potential relative to the level thereof immediately after the injury.

Claims Rejections - 35 U.S.C. §§ 102 and 103

Claims22, 24-29, 38, and 39 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Davis et al. (Journal of Spinal Disorders, 1990; 3(4): 299-306).

Claims 23, 30-37, and 40-43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis et al. (Journal of Spinal Disorders, 1990; 3(4): 299-306) in view

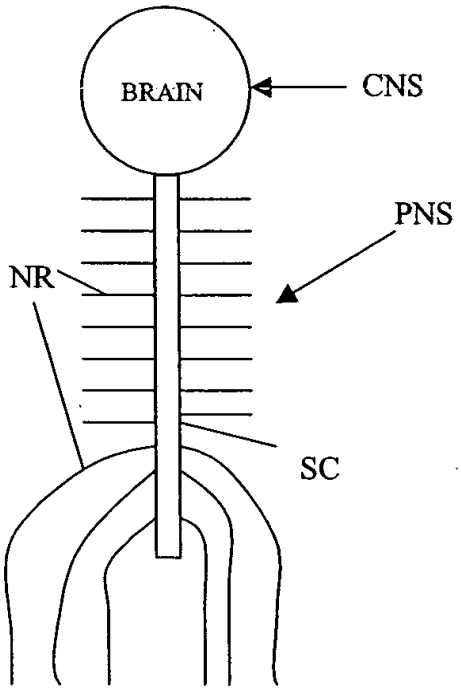
of Brown (Clinical Orthopedics and Related Research, 1977; 129: 72-78) and Potter et al. (Clin. Invest. Med., 19(4), Suppl.: S80, #533).

Applicants respectfully traverse the rejection of claims 22, 24-29, 38, and 39 under 35 U.S.C. § 102(b) as being anticipated by Davis et al. (Journal of Spinal Disorders, 1990; 3(4): 299-306). As pointed out by the Examiner, that reference teaches the deposition of methylpregnisolone containing PEG 3350 on an exposed nerve root during a spinal lumbar surgery for disc excision and retraction of the nerve root with incision. That description of the teachings of Davis et al. is correct. However, the Examiner goes on to characterize this incision as being a form of spinal cord injury. That characterization is incorrect. Davis et al. teach ***nothing*** about the application of PEG to an injured spinal cord for the simple reason that a nerve root is located ***outside of the spinal column*** and is part of the ***peripheral nervous system***.

The nerve fibers of the peripheral nervous system are ***vastly different*** from the nerve fibers of the central nervous system, particularly including the spinal cord. The anatomy of nerves of the peripheral nervous system is different from the anatomy of nerves in the central nervous system (brain and spinal cord). Severing of or injury to the nerve roots ***never*** results in paralysis, whereas injury to the spinal cord frequently does result in paralysis. Moreover, the nerves of the peripheral nervous system are capable of ***regeneration*** whereas the nerves of the central nervous system, particularly the spinal cord are ***not*** capable of regeneration. Accordingly, it is not surprising that nerve roots, which are fibers located outside of the spinal cord and which are not part of the spinal cord, might experience some restoration after an injury and upon proper treatment. However, that a treatment of an injured nerve root might have a positive effect on the nerve root is ***no indication*** whatsoever that the same treatment will have any effect whatsoever on a spinal cord injury. As stated in the Declaration of applicant Dr. Richard B. Borgens submitted in response to the previous Office Action, any restoration of nerve

function to an injured spinal cord *in vivo* is a surprising and unexpected result. That the application, to an injured nerve root, of a composition incidently containing PEG has a therapeutic effect on the nerve root provides no expectation whatsoever that the purposeful application of PEG to an injured spinal cord would have any therapeutic effect on the spinal cord.

To clarify the differences between the nerve roots and the spinal cord, applicants provide the following drawing.



Further to the discussion above, the brain and the spinal cord SC form the central nervous system CVS, while the nerve roots NR are part of the peripheral nervous system PNS and are located outside of the spinal cord SC. (The peripheral nervous system PNS additionally includes other nerves in the body.) The spinal cord SC is located completely inside of the vertebral column (not separately shown). Fibers of the spinal cord SC may be processes of nerve cells whose cell bodies are located along, but outside of, the spinal cord SC. Those cells have nerve processes which together with nerve processes leaving

the spinal cord SC are the nerve roots NR. These extend from the spinal cord SC to peripheral areas of the body at each vertebral level.

This characterization of the spinal cord and nerve roots may be easily verified by consulting any reference work on anatomy. Attached hereto, for example, as APPENDIX B is a print-out of a page from the World Wide Web, at the Web address www.spine-health.com/topics/anat/a04.html. The description on that Web page indicates that the nerve roots are different from the spinal cord and extend outwardly from the spine: "The spinal cord does not run through the lumbar spine. After the spinal cord stops in the lower thorasic spine, the nerve roots come off the bottom of the cord like a 'horse's tail.'" Also: the "nerve roots run through the bony canal, and at each level a pair of nerve roots exists the spine."

Also attached hereto as APPENDIX C is a copy of an excerpt from "Wheeless' Textbook of Orthopaedics," also taken from the World Wide Web at site www.medmedia.com/o11/44.htm. The description of spinal nerves indicates that the nerves leave the spinal column or vertebral canal through intervertebral foramina.

It is to be noted, with respect to the teachings and implications of Davis et al., that one of ordinary skill in the art would not, on the basis of that reference, apply a polyalkylene to a spinal cord injury for a therapeutic purpose. The purpose of PEG in the methylpregnisolone composition is to increase solubility . PEG is used ubiquitously in medical and cosmetic applications for this purpose: to bond to an insoluble chemical composition in order to render that composition soluble in aqueous solutions.

As pointed out in a prior Amendment, the present invention has evidenced unexpected activity in restoring nerve function and behavioral recovery in mammalian patients. The present invention could not possibly be predicted from the prior art and represents an unexpected result over the disclosure of the prior art. In the present invention, as described in the examples of the specification, a dramatic response to treatment with PEG was realized in experimental animals (guinea pigs). In the present invention 100% of experimental animals treated with PEG evidenced substantial return of cord nerve impulse conduction vs. 0% of controls and 90% PEG-treated guineas pigs exhibited a return of behavior vs. 17% of controls. These results represent an unexpected

result and evidence that the present method exhibits great potential to treat patients who have suffered spinal cord injury.

As noted above, the teachings of Davis et al. could not possibly provide any level of expectation which might approximate the *in vivo* treatment of an injured spinal cord. The differences between the spinal cord (CNS) and nerve roots (PNS) are too substantial to imply or suggest treatment of an injured spinal cord as compared to the treatment of exposed nerve roots.

Turning now to the Examiner's rejection of the claims which utilize a potassium channel blocker in combination with an polyalkylene glycol to synergistically treat spinal cord injury, applicants respectfully submit that the disclosures of Potter et al. and/or Brown and the disclosure of Davis et al. fail to render those claims obvious. As discussed hereinabove, the present invention makes use of polyalkylene glycol compounds to treat spinal cord injury in mammalian patients. As discussed, the teachings and implications of Davis et al. in no way renders the present invention anticipated or obvious. The disclosures of Potter et al. and Brown are essentially inapposite to the present invention inasmuch as these references do not in any way cure the deficiencies of the prior art. Potter teaches the use of 4-aminpyridine in spinal cord injuries but fails to even mention polyalkylene glycol. Neither Potter et al. nor Brown recognizes the unexpected properties the polyalkylene glycols exhibit in treating spinal cord injury. Neither of these references even mentions polyalkylene glycols as a possible treatment for spinal cord injury. Because of the deficient disclosures of Potter et al. and Brown, it is respectfully submitted that the claimed invention is patentable over these references.

It is to be noted that the amendments made herein could not have been made earlier owing to the fact that the rejections addressed herein were made only in the final Office Action. The amendments made herein are deemed to reduce the issues for appeal: all of the § 112 issues are believed to be overcome by the amendments made herein.

For the above reasons, applicants respectfully assert that the claims set forth in the amendment to the application of the present invention are now in compliance with 35

U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

COLEMAN SUDOL SAPONE, P.C.

Dated: February 22, 2002

By: _____

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: "Commissioner for Patents, Washington, D.C. 20231" on February 22, 2002.

_____

R. Neil Sudol, Reg. 31,669

APPENDIX A

Amend claim 22 as follows:

22. (Once Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting [said] the injured spinal cord [as soon as is possible and] within a period no greater than about 24 hours after said injury with [an effective amount of] a C_1-C_{10} polyalkylene glycol[, said method resulting in at least partial restoration of nerve function] in an amount effective to increase a compound action potential in said injured spinal cord relative to a level of said compound action potential immediately after said injury and [an increased] to increase behavioral recovery after said spinal cord is treated.

Amend claim 30 as follows:

30. (Once Amended) The method according to claim 22, wherein said polyalkylene glycol is polyethylene glycol and wherein said method further comprises the step of contacting said injured spinal cord with [an effective amount of] a potassium channel blocker [before, during or after] in the form of 4-aminopyridine in an effective amount and within an effective time of contacting said spinal cord with said [polyalkylene] polyethylene glycol[, said method resulting in] so as to produce a synergistic increase in restoration of nerve function and reflex behavior in said patient.

Amend claim 38 as follows:

38. (Once Amended) A method of treating a mammalian patient having suffered an injury to its spinal cord, said method comprising contacting [said] the injured spinal cord [as soon as is possible and] within a period no greater than about 24 hours after said injury with [an effective amount of] polyethylene glycol[, said method resulting in at least partial restoration of nerve function] in an amount effective to increase a compound action potential in said injured spinal cord relative to a level of said compound action potential immediately

after said injury and [an increased] to increase behavioral recovery after said spinal cord is treated.

Amend claim 40 as follows:

40. (Once Amended) The method according to claim 38 further comprising the step of [contact] contacting said injured spinal cord with [an effective amount of] a potassium channel blocker [before, during or after] in the form of 4-aminopyridine in an effective amount and within an effective time of contacting said spinal cord with said polyethylene glycol.

APPENDIX B

FIGURES

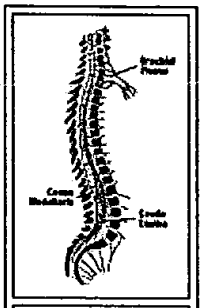

Fig 1: Spinal Cord and Nerve Roots (larger view)

Fig 2: Distribution of Disc Herniations (larger view)

Overview

Spinal cord and nerve roots

The spinal cord comes off the base of the brain, runs throughout the cervical and thoracic spine, and ends at the lower part of the thoracic spine. Therefore, spinal cord damage may accompany trauma or diseases of the cervical or thoracic spine.

The spinal cord does not run through the lumbar spine. After the spinal cord stops in the lower thoracic spine, the nerve roots come off the bottom of the cord like a "horse's tail" (cauda equina) (see Figure 1).

Therefore, because the lumbar spine has no spinal cord and comprises a large amount of space for the nerve roots, even serious conditions (such as a large disc herniation) are unlikely to cause paraplegia (loss of motor function in the legs).

The nerve roots run through the bony canal, and at each level a pair of nerve roots exits from the spine.

- In the cervical spine, the nerve root is named for the lower segment that it runs between (e.g. C6 at C5-C6 segment).
- In the lumbar spine, the nerve is named for the upper segment that it runs between (e.g. L4 at L4-L5 segment)

The nerve passing to the next level runs over a weak spot in the disc space, which is the reason discs tend to herniate (extrude) right under the nerve root and can cause leg pain (radiculopathy or sciatica).

- Cervical disc herniations tend to irritate the nerve exiting at a particular level (e.g. C6 at C5-C6)
- Lumbar disc herniations tend to irritate the nerve that lies across a particular level (e.g. L5 at L4-L5) (Figure 2)
- Thoracic disc herniations are very rare

Sometimes, a herniated disc will cause only leg/arm pain and not low back/neck pain, and may initially be thought to be a problem with the leg/arm.

- Arm pain from a cervical disc herniation is usually accompanied by numbness/tingling and runs to the fingers
- Leg pain from a lumbar disc herniation will usually run below the knee, and possibly to the foot, and may be accompanied by numbness

The two nerves most commonly pinched are L5 (lumbar 5) and S1 (sacral 1). The L5 nerve supplies the nerves to the muscles that raise the foot and big toe, and consequently, impingement of this nerve may lead to weakness in these muscles. Likewise, S1 impingement can lead to weakness with the large gastronemius muscle in the back of the calf, causing difficulty with foot push off (see Figure 3).

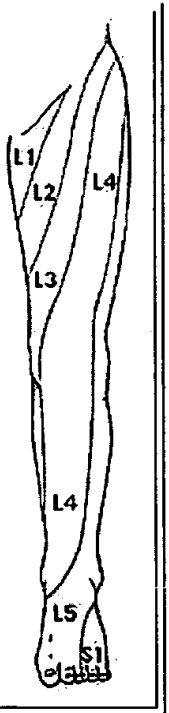

Fig 3: Distribution of Skin Innervation (larger view)

Numbness for L5 runs over the top of the foot and for S1 it runs on the outside of the foot. The S1 nerve root also supplies innervation for the ankle jerk (tap on the achilles tendon and the foot goes down), and a loss of this reflex indicates S1 impingement, although it does not create loss of function.

Most cervical pathology will lead to pinching of either C6 or C7 nerve roots, although sometimes C5 or C8 may be pinched. Depending on which nerve root is pinched, the following symptoms are likely:

- C5 - shoulder pain, deltoid weakness, and possibly a small area of numbness in the shoulder. On physical exam, a patient's biceps reflex may be diminished.
- C6 - weakness in the biceps and wrist extensors, and pain/numbness that runs down the arm to the thumb. On physical exam, the brachioradialis reflex (mid-forearm) may be diminished.
- C7 - pain/numbness that runs down the arm to the middle finger. On physical exam, the triceps reflex may be diminished.
- C8 - hand dysfunction (this nerve supplies innervation to the small muscles of the hand). Pain/numbness can run to the outside of the hand (little finger) and impair its reflex.

The nerve consists of one long cell from the back/neck down to the foot/hand, so the nerves tend to heal slowly. They heal from the top down, and depending on how much damage is done at the time the nerve becomes impinged, it may take weeks to months to heal.

Treatment of neural impingement is directed at relieving the pain and then allowing the nerve to heal on its own. Nerves need both inflammation and pressure to be painful, so either relieving the inflammation or the pressure can relieve the pain.

Back to anatomy

Next: Muscles

SEE MORE

Animation of:
- Spinal anatomy

Related information:
- Where does it hurt? Categories of back pain
- Common causes
- Types of lower back pain
- Types of neck pain

APPENDIX C

Main Menu Home Page

Spinal Cord and Meninges:

- See: Neuro Exam:

- **Discussion:**
  - vertebral canal houses the spinal cord and its meningeal coverings;
  - medulla oblongata is continuous w/ spinal cord at foramen magnum, & spinal cord usually ends inferiorly at level of 1st or 2nd lumbar vertebra;
  - **filum terminale:**
    - at tapered inferior end of spinal cord, cord of filum terminale, continues inferiorly to merge w/ periosteum on dorsum of coccyx;
  - **spinal dura:**
    - separated from inner surface of bones forming vertebral canal by epidural space containing fat and a rich plexus of veins;
    - dural sac continues inferiorly to middle of second sacral vertebra;
    - pia mater is closely attached to spinal cord, & subarachnoid space, containing cerebrospinal fluid, is space between it & arachnoid which lies on inner surface of dura;
  - **spinal nerves:**
    - leave vertebral canal through intervertebral foramina;
    - each nerve is formed by union of a dorsal root and a ventral root, usually at intervertebral foramen;
    - subarachnoid space is prolonged in a duralarachnoid sheath around each dorsal and ventral root, roughly to the level of union of roots;
    - since cord is shorter than vertebral column, nerves slope inferiorly from their origin to appropriate intervertebral foramina;
    - below inferior end of cord, duralarachnoid sac contains a leash of nerve roots and the filum terminale;
    - this complex constitutes the cauda equina;
  - **cervical spinal nerves:**
    - there are eight pairs of cervical nerves & seven cervical vertebrae, hence cervical nerves are numbered according to vertebra above which they emerge;
    - 5th cervical nerve emerging above 5th vertebra;
    - 8th cervical nerve emerges between C7 & T1;
  - **thoracic cord & spinal nerves:**
    - since thoracic nerves are numbered according to the vertebra below which they emerge, protrusion of the disc between the 5th and 6th thoracic vertebrae would compress the roots of the 5th thoracic nerve;
  - **lumbar spinal nerves:**
    - intervertebral foramina in lumbar region are larger than lumbar nerves;
    - each nerve emerges thru upper part of foramen and lies against body of vertebra above;
    - protrusion of lumbar disc will not affect nerve corresponding in number to that intervertebral discs (that nerve emerges above the disc);
    - protruded disc usually compresses next lower nerve as that nerve crosses level of disc in its path to its foramen;
      - hence, protrusion of fifth lumbar disc usually affects S1 instead of L5;
  - **myelomere:**
    - because spinal cord is shorter than vertebral column, level of emergence of spinal nerve is below level of segment of spinal cord from which it arises;
    - myelomere, or segment of cord from which nerve root arises, lies one level above the same numbered vertebral body;
    - between C2 and T10 , number of cord segment is the number of spinous process, plus two;
      - T5 myelomere lies at the level of the T4 vertebral body;
      - T6 overlies T8 thoracic segment of spinal cord;
      - lumbar and sacral myelomeres are concentrated between T11 and L1 vertebral bodies;
        - spinous processes of T11 & T12 overlie 5 lumbar segments;
      - conus medullaris is usually found at level of L1-L2 intervertebral disc & contains myelomeres of the 5 sacral nerve roots;
      - L1 spinous process overlies five sacral segments of the spinal cord;
  - **cord injuries:**

- neurologic injury above the T-10 are related purely to cord damage;
- injuries occuring between T-10 and L1 have mixed injury patterns;
- injuries occuring below L1, cause purely peripheral nerve root damage;

References:

Organization of intrathecal nerve roots at the level of the conus medullaris.

Outside Links

The Global Spinal Cord '97
